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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/545,190	11/09/2005	Peter Jan Zimmermann	26887U	1362

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EXAMINER	
MURRAY, JEFFREY H	
ART UNIT	PAPER NUMBER
1624	
MAIL DATE	DELIVERY MODE
04/16/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/545,190	ZIMMERMANN ET AL.	
	Examiner	Art Unit	
	JEFFREY H. MURRAY	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 12-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 12-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/09/2005 & 12/04/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to an application filed on August 11, 2005. There are thirteen claims pending and thirteen claims under consideration. Claims 10 and 11 have been cancelled. This is the first action on the merits. This invention relates to novel compounds, which are used in the pharmaceutical industry as active compounds for the production of medicaments.

Priority

2. Acknowledgment is made of Applicant's claim for foreign priority. This application, U.S. Application No. 10/545,190, filed on August 11, 2005, is a national stage application of PCT/EP04/50135 filed on February 16, 2004 which claims foreign priority to European Application No. 03003652.9, filed February 18, 2003.

Specification

3. The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
    (1) Field of the Invention.

(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

4. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any of the errors of which applicant may become aware of in the specification.

Claim Rejections - 35 USC § 112, 1st paragraph

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-9 and 12-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound, pharmaceutical composition or a pharmaceutically acceptable salt thereof where R_1, R_2, R_4, and R_5 are alkyl; X is NH; and Ar is a phenyl ring, does not reasonably provide enablement for a solvate, hydrate, hydrate of a salt or solvate of a salt. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

7. The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known

in the art without undue experimentation. (*United States v. Teletronics* Inc., 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors (See *Ex parte Forman* 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

These factors include the following:

1) *Amount of guidance provided by Applicant.* Applicant has provided no guidance, examples, or provided any chemical or biological data and/or testing results of any compounds or compositions which are other than the above mentioned compounds or compositions or any hydrates, solvates, hydrates of salts or solvates of salts in the current application.

The scope of "hydrate," "solvate," "hydrate of a salt" and "solvate of a salt" are not adequately enabled or defined. Applicants provide no guidance as how the compounds are made more active *in vivo*. Solvates and hydrates cannot be predicted and therefore are not capable of being claimed if the applicant cannot properly enable a particular solvate, hydrate, solvate of a salt or hydrate of a salt.

> "Predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of related compounds. Certain molecular shapes and features favor the formation of crystals without solvent; these compounds tend to be stabilized by efficient packing of molecules in the crystal lattice, whereas other crystal forms are more stable in the presence of water and/or solvents. There may be too many possibilities so that no computer programs are currently available for predicting the crystal structures of hydrates and solvates. (Vippagunta et. al. Advanced Drug Delivery Reviews 48 (2001) 3-26.)

2) Unpredictability in the art. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. (USPQ 18, 24 (CCPA 1970). See *In re Fisher*, 427 F.2d 833, 839, 166.

Chemistry is unpredictable. See *In Re Marzocchi and Horton* 169 USPQ at 367 paragraph 3:

> "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work .....Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious)..." Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim pg. IX of Preface.

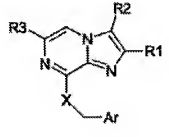
3) *Number of working examples.* The compound core depicted with specific substituents represents a narrow subgenus for which applicant has provided sufficient guidance to make and use; however, this disclosure is not sufficient to allow extrapolation of the limited examples to enable the scope of the compounds instantly claimed or preventive agents. Applicant has provided no working examples, of any

compounds or compositions which are other than the above mentioned compounds or compositions or any hydrates, solvates, hydrates of salts or solvates of salts in the current application.

Within the specification, "specific operative embodiments or examples of the invention must be set forth. Examples and description should be of sufficient scope as to justify the scope of the claims. *Markush* claims must be provided with support in the disclosure for each member of the *Markush* group. Where the constitution and formula of a chemical compound is stated only as a probability or speculation, the disclosure is not sufficient to support claims identifying the compound by such composition or formula." See MPEP 608.01(p).

4) *Nature of the invention.* The nature of this invention relates to novel compounds, which are used in the pharmaceutical industry as active compounds for the production of medicaments.

5) Scope of the Claims. The scope of the claims is all of the compounds represented by general formula 1:



Where R_1, R_2, R_4, and R_5 are alkyl; X is NH; and Ar is a phenyl ring, thus the scope of the claims is very broad.

6) *Level of skill in the art.* The artisan using Applicants invention would be a chemist with a Ph.D. degree, and having several years of bench experience.

MPEP §2164.01 (a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here that Applicant is not enabled for making these compositions.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. Claims 1-9 and 13-15 are rejected under 35 U.S.C. 103(a) as being unpatentable

over Amin et. al. (WO9928322) in view of Patani et. al. The current application recites a variety of imidazopyrazine compounds, pharmaceutical compositions comprising the compounds and the use of the compounds as inhibitors of gastric acid secretion.

11. Amin, et. al., teaches compounds which are similar in scope to the current application. Within Amin, et. al., similar structures are seen which also teach imidazopyrazine compounds as inhibitors of gastric acid secretion.

Amin, et. al., has as an identical core structure to the current patent application with one major difference. Amin, et. al., only permits the R5 group (R3 in the current application) to be a hydrogen or alkyl group, where the current application contains an R3 group which cannot be a hydrogen or alkyl group.

The reference, Patani et. al., page 3147-8, describes in detail the concept of bioisosteres. In medicinal chemistry, bioisosteres are substituents or groups with similar physical or chemical properties that may impart similar biological properties to a chemical compound. In drug design, the purpose of exchanging one bioisostere for another is to enhance that desired biological or physical properties of a compound without making significant changes in chemical structure (Lipinski et. al., p. 283-291).

Patani states, "The bioisostere rationale for the modification of lead compounds is traced back to the observation by Langmuir in 1919 regarding the similarities of various physiochemical properties of atoms, groups, radicals, and molecules. Langmuir compared the physical properties of various molecules such as N_2, and CO, N_2O and CO_2 and N_3- and NCO- and found them to be similar. On the basis of these similarities, he identified 21 groups of isosteres.

A further extension to this concept came about in 1925 with Grimm's Hydride Displacement Law. This law states: "Atoms anywhere up to four places in the periodic system before an inert gas change their properties by uniting with one to four hydrogens, in such a manner that the resulting combinations behave like pseudoatoms, which are similar to elements in the groups one to four places, respectively, to their right. Each vertical column below, according to Grimm, would represent a group of isosteres:"

C	N	O	F	Ne	Na
	CH	NH	OH	FH	--
		CH_2	NH_2	OH_2	FH_2^+
			CH_3	NH_3	OH_3^+
				CH_4	NH_4^+

Grimm's Hydride Displacement Law...outline a series of replacements which have been referred to as classical bioisosteres." (Patani et. al. p.3148)

Patani et. al. gives a solid reason to attempt to replace certain atoms with pseudoatoms. We then apply this logic to the Amin, et. al., prior art reference. When we look at Amin, et. al., the compounds are permitted to contain a halo group in the 7-position of the imidazopyrazine compound. When Patani et. al., is taken into account, one can look at the above chart and see that in column 3, an -F-, -OH-, $-NH_2$-, and $-CH_3$ all fall within the same column in Grimm's Hydride Displacement Law. This allows us to presume that if we were to replace any of these three moieties with the other, we would get similar physiochemical properties.

Relating this information to the Amin, et. al., publication, the compounds of Amin, et. al. which may contain a methyl group in the 7-position of the imidazopyrazine could be replaced with a fluoro group of these compounds with a $-CH_3$ group following

Grimm's Hydride Displacement Law, we would then obtain compounds being used for the same purpose that would render obvious the claims of the current application.

It would have been obvious to a person of ordinary skill in the art at the time of the invention to try replacing an alkyl group located in the 7-position of the imidazopyrazine ring in Amin, et. al., with a $-CH_3$ moiety in an attempt to enhance activity and afford a positive benefit from the replacement for use in a similar or identical purpose. A person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to a reasonable expectation of success, it is likely the product in not one of innovation but of a product obtained by ordinary skill and common sense.

Conclusion

12. Claims 1-9 and 12-15 are rejected.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey H. Murray whose telephone number is (571) 272-9023. The examiner can normally be reached on Mon-Thurs. 7:30-6pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached at 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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